Contains Nonbinding Recommendations

Draft Guidance on Leuprolide Acetate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Leuprolide Acetate

Form/Route: Injectable Depot

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, randomized, parallel, in vivo
   Strength: 30 mg/vial
   Subjects: Prostatic carcinoma patients undergoing initial therapy.
   Additional Comments: The test and reference groups should be balanced with respect to patient disease progression and treatment history. Furthermore, the treatment regimen during the study should be identical between the test and reference groups.

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2. Type of study: Fasting
   Design: Single-dose, randomized, parallel, in vivo
   Strength: 45 mg/vial
   Subjects: Prostatic carcinoma patients undergoing initial therapy.
   Additional Comments: The test and reference groups should be balanced with respect to patient disease progression and treatment history. Furthermore, the treatment regimen during the study should be identical between the test and reference groups.

Analytes to measure (in appropriate biological fluid): Leuprolide in serum

Bioequivalence based on (90% CI): Leuprolide

The 90% confidence intervals of the following PK parameters must meet the acceptable limits of [80.00-125.00]: Log-transformed $AUC_{7\text{-}t}$, AUC_t, $AUC_{0\text{-}\infty}$, and C_{max},

where $AUC_{7\text{-}t}$ is the area under the plasma-concentration vs. time curve from 7 days to the last sampling time point, AUC_t is the area under the curve from 0 to the last sampling time point, $AUC_{0\text{-}\infty}$ is the area under the curve from 0 to infinity, and C_{max} is the maximum plasma concentration.

Waiver request of in vivo testing: 11.25 mg/vial-3 month and 22.5 mg/vial based on (1) an acceptable bioequivalence study on 30 mg/vial strength (2) acceptable dissolution testing across all strengths (3) qualitative (Q1) and quantitative (Q2) sameness to the respective RLD strength.

Please note that Leuprolide Acetate for Depot Suspension, 11.25 mg/vial-3 month, and Leuprolide Acetate for Depot Suspension, 22.5 mg/vial, 30 mg/vial, and 45 mg/vial, are the subject of two separate reference products. Two separate applications comparing to the appropriate reference product must be submitted if requesting a waiver for the 11.25 mg/vial- 3 month product.

An applicant may request a waiver of in vivo bioequivalence testing for the 11.25 mg/vial-3 month, and 22.5-mg/vial strengths provided that it (1) submits an ANDA containing an acceptable in vivo study on the 30-mg/vial strength; (2) if necessary, cross-references the ANDA for the 30 mg/vial strength; and (3) documents Q1 and Q2 sameness to the respective RLD strength. Please refer to the Guidance for Industry, *Variations in Drug Products That May Be Included in a Single ANDA*, located at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072892.pdf.

Dissolution test method and sampling times:

Please note that the **Dissolution Method Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 vials each of all strengths of the test and reference products. Specifications will be determined upon review of the application.